REMARKS

The Office asserts that a process that includes selectively hydrogenating the carbon-carbon double bonds of pseudoionone to form tetrahydrogeranylacetone is obvious over a process that includes hydrogenating an olefinic material (Kaibel - U.S. 5,939,589) in combination with a process that includes hydrogenating a compound having one C-C double bond and one carbonyl bond (Broecker - U.S. 6,150,564). Applicants traverse the rejection for the reason, *inter alia*, that Broecker does not disclose or suggest that improved selectivity may be obtained when hydrogenating molecules having more than one C-C unsaturation.

Applicants submit that it is readily recognized by those of skill in the art that the rate of hydrogenation of different C-C unsaturations varies with the chemical environment of the C-C unsaturation. Applicants submit herewith pages 189-190 of "Ullmann's Encyclopedia of Industrial Chemistry, 5th Edition", Volume A10 (1987) which disclose the following with respect to the selectivity of C-C double bond hydrogenation in a molecule that has several double bonds in different chemical environments:

> A fatty acid with several double bonds, such as linolenic acid…, is hydrogenated more quickly to linoleic acid ($C_{18:3}$) or oleic acid ($C_{18:2}$) than is linolenic acid to oleic acid ($C_{18:1}$) or oleic acid to strearic acid ($C_{18:0}$).

See page 189 right hand column. In the above quoted text ($C_{18:X}$) represents a 18 carbon molecule with "X" C-C double bonds.

Ullmann's therefore shows that the reactivity of all double bonds cannot be treated equally and that the rate of hydrogenation (e.g., the ease of hydrogenation) of the C-C double bonds of an organic molecule depend at least in part on the chemical environment around the C-C double bond.

Broecker, at best, discloses that selectivity of C-C vs C-O hydrogenation may be improved for molecules that have only a single C-C unsaturation (and therefore only a single rate of hydrogenation). For example:

> The novel process may in principle be used for all α,β-unsaturated carbonyl compounds of the formula (I), the shortened reaction time improving the selectivity with respect to hydrogenation of the double bond, <u>i.e. the individual reaction with the larger rate constant</u>. In a preferred embodiment, the starting material citral is converted to citronellal.

See column 2, lines 28-34 of <u>Broecker</u> (underlining added for emphasis).

Even if <u>Broecker</u> may suggest that the prior art process may be carried out on molecules having more than one C-C double bond (e.g., where R1 is an olefinic moiety), <u>Broecker</u> does not disclose or suggest that the C-C double bonds of the olefinic moiety have different rates of hydrogenation (e.g., having different rate constants). <u>Broecker</u> further does not disclose that the other C-C double bonds may be selectively hydrogenated with respect to the C-O double bond.

The psuedoionone of the present claims has three different C-C double bonds each having a different rate/ease of hydrogenation. The preference to hydrogenate only the C-C double bonds over the C-O double bonds would not have been foreseen by <u>Broecker</u>'s disclosure which is relevant to molecules containing one C-C double bond. The extra selectivity, e.g., increased selectivity, of the claimed process was therefore not foreseeable from the prior art relied on by the Office.

Applicants draw the Office's attention to new dependent Claims 23-26 which require certain degrees of hydrogenation conversion and/or selectivity. In contrast, <u>Broecker</u> discloses a hydrogenation of citral which is carried out with a selectivity of 94% and a conversion of 99.5%, substantially less than the 96% selectivity and 99.9% conversion of the new dependent claims.

Applicants further traverse the rejection on the grounds that the Office has not shown nor provided any reasoned technical basis why it would be obvious to selectively hydrogenate the C-C unsaturations of a compound having a multiple C-C unsaturations without hydrogenating a carbonyl moiety in the same molecule. Applicants submit that it is

readily recognized by those of skill in the art that the ease of hydrogenation of different functional groups varies with the nature of the unsaturation. Applicants submit herewith pages 1093-1096 of "Advanced Organic Chemistry, 3rd Edition", J. March, Ed., (1985) which show that conjugated olefins are more difficult to hydrogenate than ketone materials of formula RCOR. Pseudoionone, the compound undergoing hydrogenation in the presently claimed process, has conjugated C-C double bonds, see the attached structure for pseudoionone obtained from www.sigmaaldrich.com. Consistent with Broecker, "Advanced Organic Chemistry" indicates that an internal unsaturation of formula RCH=CHR undergoes hydrogenation before a carbonyl-containing compound such as a ketone of formula RCOR.

The Office appears to assume that Broecker's disclosure of the selective hydrogenation of a single internal olefinic bond preferential to the hydrogenation of a carbonyl material is evidence that all of the C-C unsaturations of pseudoionone would necessarily be hydrogenated before the carbonyl moiety of pseudoionone. Applicants submit that the Office failed to take into consideration information regarding the ease of hydrogenation of different unsaturated materials in comparison to the ease of saturation nof ketonic groups, e.g., such as the attached ease of hydrogenation information provided in "Advanced Organic Chemistry".

Applicants submit that it does not necessarily follow from Broecker's disclosure that all unsaturated carbonyl compounds undergo complete hydrogenation of any C-C double bonds before hydrogenation of any C-O double bonds. In fact, "Advanced Organic Chemistry" teaches just the opposite; namely, that compounds having conjugated C-C unsaturation are much more difficult to hydrogenate in comparison to carbonyl-containing compounds such as ketones of formula RCOR. If the hydrogenation of pseudoionone occurred in the order disclosed in "Advanced Organic Chemistry" the carbonyl moiety would undergo hydrogenation before the C-C unsaturated double bonds of the conjugated

unsaturated system. Consequently it would be impossible to obtain tetrahydrogeranylacetone by hydrogenating pseudoionone. However, as Applicants have shown, it is possible to obtain tetrahydrogeranylacetone from pseudoionone, e.g., when the hydrogenation is carried out with the particular device recited in the present claims.
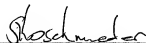
Applicants submit that those of ordinary skill in the art would not expect to obtain tetrahydrogeranylacetone from pseudoionone in view of Broecker or Kaibel in view of the ease of hydrogenation information disclosed in "Advanced Organic Chemistry". Applicants request withdrawal of the rejection.

Applicants draw the Office's attention to new dependent Claims 19-22 drawn to different embodiments of the invention. In particular, Claims 19 and 21 state that the pseudoionone comprises essentially no amount of a diluent. In contrast, Broecker discloses the hydrogenation of citral-containing mixtures that contain 27 wt.% of a diluent such as methanol (see the examples of Broecker). Applicants submit that new dependent Claims 19 and 21 are further patentable over the prior art relied upon by the Office on the ground that those of ordinary skill in the art would have no reason to believe that carrying out the hydrogenation of an essentially pure pseudoionone solution would be an effective means of obtaining tetrahydrogeranylacetone.

For the reasons discussed above in detail, Applicants submit that all now-pending claims are in condition for allowance and respectfully request the mailing of a Notice of Allowance acknowledging the patentability of the presently claimed subject matter.

Respectfully submitted,

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22850

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(OSMMN 03/06)
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11

Ullmann's Encyclopedia of Industrial Chemistry

Fifth, Completely Revised Edition

Volume A 10:
Ethanolamines to Fibers, 4. Synthetic Organic

Executive Editor: Wolfgang Gerhartz
Senior Editor: Y. Stephen Yamamoto
Editors: Lydia Kaudy, James F. Rounsaville,
Gail Schulz

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Vol. A 10

Contents

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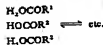
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$$S–S–S \; + \; O–O–O$$
$$50\% \qquad 50\%$$

$$\downarrow$$

S–S–S	S–O–S	O–S–S	S–O–O	O–S–O	O–O–O
12.5%	12.5%	25%	25%	12.5%	12.5%

S = stearic acid, O = oleic acid
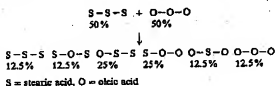
In *directed interesterification*, the temperature is reduced to such an extent that the highest melting glycerides are continously frozen out of the reaction mixture, in turn continuously shifting the reaction equilibrium. In this way a fat can be separated into higher and lower melting fractions. The higher melting fraction contains the glycerides of saturated fatty acids (stearin fraction), whereas the glycerides of unsaturated fatty acids are found in the lower melting fraction (olein fraction). Directed interesterification of stearodiolein can yield 33.3% of tristearin and 66.7% of triolein:

$$O–S–O$$
$$\downarrow$$
$$S–S–S \qquad O–O–O$$
$$33.3\% \qquad 66.7\%$$

S = stearic acid, O = oleic acid
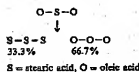
3.3. Hydrogenation

The double bonds in a fatty acid chain can be wholly or partially saturated by addition of hydrogen in the presence of a suitable catalyst such as nickel, platinum, copper, or palladium. Hydrogenation always leads to an increase in melting point and is therefore also called "hardening". Partial hydrogenation can lead to isomerization of cis double bonds to trans double bonds.

The catalyst, the oil, and the hydrogen must be brought into mutual contact under suitable temperature and pressure conditions. The reaction rate depends on mixing intensity, the type of oil or fat, temperature, catalyst activity, and concentrations of catalyst and dispersed hydrogen. Hydrogenation is an exothermic process. Industrial nickel catalysts are generally obtained by precipitation of nickel hydroxide or carbonate on kieselguhr, silica gel, alumina, or similar car-

riers, followed by reduction to metallic nickel, or by in situ production of metallic nickel from nickel formate. Such heterogeneous catalysts have a large activated surface. During hydrogenation the double bonds form transient complexes with the active centers of the catalyst. These complexes disintegrate after reaction of the double bonds with hydrogen, leaving the catalyst in its original form [26]. The active centers of the catalyst can be inactivated or poisoned by a number of compounds such as phospholipids, sulfur compounds, organic acids, and oxidized lipids.

A fatty acid with several double bonds, such as linolenic acid ($C_{18:3}$), is hydrogenated more quickly to linoleic acid ($C_{18:2}$) or oleic acid ($C_{18:1}$) than is linoleic acid to oleic acid or oleic acid to stearic acid ($C_{18:0}$). The reaction sequence occurring during hydrogenation can be represented schematically as follows:

$$C_{18:3} \xrightarrow[+H_2]{k_3} C_{18:2} \xrightarrow[+H_2]{k_2} C_{18:1} \xrightarrow[+H_2]{k_1} C_{18:0}$$
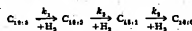
The term selectivity is used to indicate which of these reactions is fastest. Selectivity I is defined as the ratio k_2/k_1; it is related to the proportion of saturated glycerides formed and to the melting behavior of the product. Selectivity II, expressed as the ratio k_1/k_2, must be as high as possible if the concentration of linoleic acid in the hydrogenated product is to be maximized [27].

Selectivity can be influenced by the catalyst type (surface area, pore size, etc.) and by altering the reaction conditions. An increase in selectivity, i.e., an increase in partial hydrogenation, promotes isomerization of cis to trans double bonds.

At temperatures above 200 °C and with a low hydrogen concentration, catalytic hydrogenation of polyunsaturated fatty acid groups can lead to the formation of traces of cyclic aromatic compounds [28].

The double bonds of substituted fatty acids such as ricinoleic acid can also be hydrogenated under suitable reaction conditions. Cyclopropane or cyclopropene groups behave as double bonds and lead to branched fatty acids on hydrogenation.

Iron pentacarbonyl and cobalt octacarbonyl are examples of homogeneous hydrogenation catalysts.

Reduction with hydrazine does not lead to isomerization; there is also no selectivity ($k_1 = k_2 = k_3$).

3.4. Isomerization

Naturally occurring fatty acids exist predominantly in the cis form. An equilibrium mixture in which the higher melting trans form predominates can be formed by heating to 100–200 °C in the presence of catalysts such as nickel, selenium, sulfur, iodine, nitrogen oxides, or sulfur dioxide.

If selenium or oxides of nitrogen and sulfur are used in the cis–trans isomerization (elaidinization) of oleic acid, there is virtually no positional isomerization. However, cis–trans isomerization of linoleic and linolenic acid leads to conjugated double bonds.

Nonconjugated systems can be isomerized into conjugated systems by heating in an alkaline solution at 200 °C (→ Fatty Acids, p. 269). If reaction times and temperatures are extended, linoleic acid can be converted into cyclohexadiene and benzene derivatives:
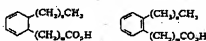
Isomerization can occur if oils and fats are heated at temperatures above 100 °C in the presence of bleaching earth, kieselguhr, or activated charcoal.

3.5. Polymerization

Dimeric, oligomeric, and polymeric compounds are formed by heating unsaturated fatty acids at 200–300 °C [29]. The rate of polymerization increases with increasing degree of unsaturation; saturated fatty acids cannot be polymerized. Thermal polymerization of polyunsaturated fatty acid groups is normally preceded by isomerization and conjugation of double bonds. Thermal polymerization involves formation of new carbon–carbon bonds by combination of acyl radicals and by Diels–Alder reactions, while oxidative polymerization involves formation of C–O–C bonds. Thermal dimerization is catalyzed by Lewis acids such as boron trifluoride; industrial processes for dimer-

izing oleic acid are based on this principle [30]. Heating of oils during refining or during household use does not lead to a significant increase in dimeric triglycerides. Up to 2% dimeric triglycerides can be encountered in fresh raffinates; these dimers are not toxic, and are largely excreted as such.

3.6. Antoxidation

Autoxidation, the oxidation of olefins with oxygen, plays a decisive role in the development of rancidity, off-flavors, and reversion flavors in oils and fats during their production and storage. Autoxidation of oil-containing products such as oilseeds and spent bleaching earths can lead to their spontaneous combustion. Autoxidation of drying oils is an important initial stage of polymerization leading to stable surface films (→ Drying Oils, A9, pp. 62–64).

Autoxidation involves the formation of a hydroperoxide on a methylene group adjacent to a double bond; this step proceeds via a free-radical mechanism:
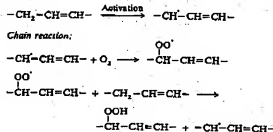
Autoxidation is characterized by an induction period during which free radicals are formed. This phase is triggered by light (photooxygenation), heat, and the presence of compounds that readily form free radicals (e.g., hydroperoxides, peroxides, and transition metals). Photooxygenation, i.e., light-induced oxidation, leads to a particularly fast buildup of radical concentration. The formation of singlet oxygen under the influence of short-wave radiation and a sensitizer such as chlorophyll or erythrosine probably plays a key role in this reaction.

The reactivity of a methylene group in forming a hydroperoxide is enhanced by a second adjacent double bond. Hence linoleic acid oxidizes 10 to 20 times faster than oleic acid. Linolenic acid reacts about three times faster than linoleic acid, since two doubly activated methylene

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ADVANCED ORGANIC CHEMISTRY

REACTIONS, MECHANISMS, AND STRUCTURE

THIRD EDITION

Jerry March

Professor of Chemistry
Adelphi University

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Harpp. Ash. Buck. Gleason. Orwig.
m. Soc., Chem. Commun. 407 (1977).

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in acetic acid. *t*-Butyl hydroperoxide has been used to oxidize certain primary amines to azoxy compounds.[411]

OS V, 341.

Reductions: Selectivity [411a]

It is often necessary to reduce one group in a molecule without affecting another reducible group. It is usually possible to find a reducing agent that will chemoselectively do this. The most common broad-spectrum reducing agents are the metal hydrides[412] and hydrogen (with a catalyst).[413] Many different metal–hydride systems and hydrogenation catalysts have been investigated in order to find conditions under which a given group will be reduced without reducing another group in the same molecule. Tables 2. 3. and 4 list the reactivity of various functional groups toward catalytic hydrogenation. LiAlH₄. and BH₃. respectively.[414,415] Table 5 shows which groups can be reduced by catalytic hydrogenation and various metal hydrides.[41b] Of course, the tables cannot be exact,

TABLE 2 The ease of reduction of various functional groups toward catalytic hydrogenation[414]

The groups are listed in approximate order of ease of reduction

Reaction	Substrate	Product	
0-84	RCOCl	RCHO	Easiest
9-48	RNO₂	RNH₂	
5-10	RC≡CR	RCH=CHR	
6-26	RCHO	RCH₂OH	
5-10	RCH=CHR	RCH₂CH₂R	
6-26	RCOR	RCHOHR	
0-80	ArCH₂OR	ArCH₃ + ROH	
6-28	RC≡N	RCH₂NH₂	
5-11			
9-43	RCOOR'	RCH₂OH + R'OH	
9-40	RCONHR'	RCH₂NHR	
5-11			Most difficult
9-39	RCOO⁻		Inert

---

⁴¹¹Kosswig. Liebigs Ann. Chem. 749, 206 (1971).

⁴¹¹ᵃFor monographs on reductions in general. see Hudlický. "Reductions in Organic Chemistry." Wiley. New York. 1984; Augustine. "Reduction." Marcel Dekker. New York. 1968. For a review. see Candlin and Rennie. in Bentley and Kirby. Ref. 12, pp. 77–135.

⁴¹²For discussions of selectivity with metal hydride reducing agents. see Brown and Krishnamurthy. Tetrahedron 35, 567–607 (1979). Walker. Chem. Soc. Rev. 5, 23–50 (1976); Brown. "Boranes in Organic Chemistry." pp. 209–251, Cornell University Press. Ithaca. N.Y.. 1972; Rerick. in Augustine. Ref. 411a. For books. see Hajós. Ref. 10 and Gaylord. Ref. 10.

⁴¹³For a discussion of catalyst selectivity for hydrogenations. see Rylander. Aldrichimica Acta, 12, 53–57 (1979).

⁴¹⁴Table 2 is from House. Ref. 10. p. 9.

⁴¹⁵Tables 3 and 4 are from Brown and Krishnamurthy. Ref. 412. pp. 213 and 232. respectively.

⁴¹ᵇThe first ten columns are from Brown and Krishnamurthy. Ref. 412. p. 604. The columns on (i-Bu)₂AlH and NaAlEt₂H₂ are from Stinson. Chem. Eng. News 58, No. 44. 19 (Nov. 3. 1980). The column on LiBEt₃H is from Brown. Kim. and Krishnamurthy. J. Org. Chem. 45, 1 (1980). For a similar table that shows additional reducing agents. see Hajós. Ref. 10. pp. 16–17. For tables showing which agents reduce a wide variety of functional groups. see Hudlický. Ref. 411a. pp. 177–200.

TABLE 3 The ease of reduction of various functional groups with LiAlH₄ in ether[418]

However, LiAlH₄ is a very powerful reagent, and much less chemoselectivity is possible here than with most of the other metal hydrides

Reaction	Substrate	Product	
6-26	RCHO	RCH₂OH	Easiest
6-26	RCOR	RCHOHR	
9-46	RCOCl	RCH₂OH	
9-43	Lactone	Diol	
0-81	RCH—CHR (epoxide)	RCH₂CHOHR	
9-43	RCOOR'	RCH₂OH + R'OH	
9-39	RCOOH	RCH₂OH	
9-39	RCOO⁻	RCH₂OH	
9-40	RCONR'₂	RCH₂NR'₂	
6-29	RC≡N	RCH₂NH₂	
9-40	RNO₂	RNH₂	
9-68	ArNO₂	ArN=NAr	Most difficult
5-10	RCH=CHR		Inert

because the nature of R and the reaction conditions obviously affect reactivity. Nevertheless, the tables do give a fairly good indication of which reagents reduce which groups.[417] LiAlH₄ is a very powerful and unselective reagent.[418] Consequently, other metal hydrides are generally used when chemoselectivity is required. As mentioned on p. 813, a number of less reactive (and more selective) reagents have been prepared by replacing some of the hydrogens of LiAlH₄ with alkoxy groups (by treatment of LiAlH₄ with ROH).[419] Most of the metal hydrides are nucleophilic reagents and

TABLE 4 The ease of reduction of various functional groups with borane[417]

It is evident that this reagent and LiAlH₄ (Table 3) complement each other

Reaction	Substrate	Product	
9-39	RCOOH	RCH₂OH	Easiest
5-12	RCH=CHR	(RCH₂CHR)₃B	
6-26	RCOR	RCHOHR	
6-29	RCN	RCH₂NH₂	
0-81	RCH—CHR (epoxide)	RCH₂CHOHR	
9-40	RCOOR'	RCH₂OH + R'OH	Most difficult
9-43, 9-46, 9-43	RCOCl		Inert

[417]See also the table in Ref. 5.
[418]For a review of LiAlH₄, see Pizey, Ref. 410, vol. 1, pp. 101–194.
[419]For a review, see Málek and Černý, Synthesis 217–234 (1972).

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TABLE 5 Reactivity of various functional groups with some metal hydrides and toward catalytic hydrogenation. "±" indicates a borderline case.

Reaction	NaBH₄ in EtOH	NaBH₄ + LiCl in diglyme	NaBH₄ + AlCl₃ in diglyme	BH₃·THF[a]	Bis-3-methyl-2-butyl-borane (disiamylborane) in THF[a]	9-BBN[a]	LiAlH(O-t-Bu)₃ in THF	LiAlH(OMe)₃ in THF	LiAlH₄ in ether	AlH₃ in THF	LiBEt₃H[a]	(i-Bu)₂AlH(DIBAL-H)	NaAlEt₂H₂	Catalytic hydrogenation
6-26 RCHO → RCH₂OH	+	+	+	+	+	+	+	+	+	+	+	+	+	+
6-26 RCOR → RCHOHR	+	+	+	+	+	+	+	+	+	+	+	+	+	+
0-84 RCHO	+[51]	+	+	−	−	+	+	+	+	+	+	+	+	+
9-46 RCOCl → RCH₂OH														
9-43 Lactone → diol	−	+	+	+	+	+	±	+	+	+	+	+	+	+
0-81 Epoxide → alcohol	−	+	+	+	±	±	±	+	+	+	+	+	+	+
9-43 RCOOR' → RCH₂OH + R'OH	−	+	+	±	−	±	±	+	+	+	+	+	+	+
9-39 RCOOH → RCH₂OH	−	+	+	+	−	±	±	+	+	+	−	+	+	−
9-39 RCHOO → RCH₂OH	−	−	−		−	±	−	+	+	+	−	+	+	−
9-40 RCONR₂ → RCH₂NR₂	−	−	−	−		−	−		+		+		+	+
0-86 RCONR₂ → RCHO	−	±	−	+	−	+	−	+	+	+	±	+	+	
6-28 RC≡N → RCH₂NH₂	−		−	+	−	±	−	+	+	+		+	+	+
RNH₂	−		−	+		±	−	+	+	+		+	+	+
9-48 RNO₂ → RNH₂	−	−	−	−	−	−	±	+	+	+	−	+	+	+
9-68 RN=NR	−	−	−				−	+	±	−		+	+	+
5-10 RCH=CHR → RCH₂CH₂R	−	−	−	+	+	+	−	−	−	−	+	−	−	+

1095

attack the carbon atom of a carbon–hetero single or multiple bond. However, BH_4^- and AlH_4^- are electrophiles (Lewis acids) and attack the hetero atom. This accounts for the different patterns of selectivity shown in the tables.

The reactions in this section are grouped into classifications based on bond charges, similar to those used for the oxidation reactions. These sections are: (A) reactions involving replacement of oxygen by hydrogen, (B) reactions in which an oxygen is removed from the substrate, (C) reduction with cleavage, and (D) reductive coupling.

A. Reactions Involving Replacement of Oxygen by Hydrogen In reactions 9-38 to 9-42, a C=O is reduced to a CH₂ group.

9-38 Reduction of Carbonyl to Methylene in Aldehydes and Ketones
Dihydro-de-oxo-bisubstitution[420]

$$R-\overset{\text{O}}{\underset{\|}{C}}-R' \xrightarrow{\text{Zn-Hg}} R-CH_2-R'$$
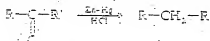
There are various ways of reducing the C=O group of aldehydes and ketones to CH₂.[427] The two most important methods are the *Clemmensen reduction* and the *Wolff–Kishner reduction* (in the Russian literature this is called the *Kizhner reaction*). The Clemmensen reduction consists of heating the aldehyde or ketone with zinc amalgam and aqueous HCl.[428] Ketones are reduced more often than aldehydes. In the Wolff–Kishner reduction,[429] the aldehyde or ketone is heated with hydrazine hydrate and a base (usually NaOH or KOH). The *Huang–Minlon modification*[430] of the Wolff–Kishner reaction, in which the reaction is carried out in refluxing diethylene glycol, has completely replaced the original procedure. The reaction can also be carried out under more moderate conditions (room temperature) in dimethyl sulfoxide with potassium *t*-butoxide as base.[431] The Wolff–Kishner reaction can also be applied to the semicarbazones of aldehydes or ketones. The Clemmensen reduction is usually easier to perform, but it fails for acid-sensitive and high-molecular-weight substrates. For these cases the Wolff–Kishner reduction is quite useful. For high-molecular-weight substrates, a modified Clemmensen reduction, using activated zinc and gaseous HCl in an organic solvent such as ether or acetic anhydride, has proved successful.[432] The Clemmensen and Wolff–Kishner reactions are complementary, since the former uses acidic and the latter basic conditions.

Both methods are fairly specific for aldehydes and ketones and can be carried out with many

[420]Reacts with solvent, reduced in aprotic solvents.

[427]Brown, Kim, and Krishnamurthy, Ref. 414. For a review of the synthesis of alkyl-substituted borohydrides, see Brown, Singaram, and Singaram, J. Organomet. Chem. 239, 43–64 (1982).

[428]Brown, Bigley, Arora, and Yoon, J. Am. Chem. Soc. 92, 7161 (1970). For reductions with thexylborane, see Brown, Heim, and Yoon, J. Org. Chem. 37, 2942 (1972).

[429]Brown, Krishnamurthy, and Yoon, J. Org. Chem. 41, 1778 (1976).

[430]See Brown, Heim, and Yoon, J. Am. Chem. Soc. 92, 1637 (1970); Ungi, "Organoboranes in Organic Synthesis," pp. 3.9–371. Marcel Dekker, New York, 1977. For a review of reductions with BF₃, see Lane, Chem. Rev. 76, 773–799 (1976); Aldrichimica Acta 16, 1–5 (1977); Brown and Krishnamurthy, Aldrichimica Acta 12, 3–11 (1979). For a review of reductions with borane-dark ethers, see Pelter, Chem. Ind. (London) 888–898 (1976).

[431]See Brown, and Yoon, J. Am. Chem. Soc. 88, 1464 (1966); 88, 1489 (1966) and Yoon, J. Am. Chem. Soc. 88, 1457 (1969).

[432]This same idea applies to reaction 8-43 to 8-45.

[For a review, see Search, in Augustine, Ref. 6, pp. 171–211.

For reviews, see Vedejs, Org. React. 22, 401–422; Vedejs and Curtis-Pulkowski, and Chem. 77, 1204–1 (1972); see Fieser and Fieser, Ref. 44, pp. 1127–1128. For a review, see Vedejs, Org. React. 22, 401–422.

Huang–Minlon, J. Am. Chem. Soc. 68, 2487 (1946); 71, 3301 (1949).

Cram, Sahyun, and Knox, J. Am. Chem. Soc. 84, 1734 (1962). Also see Grundon, Henbest, and Scott, J. Chem. Soc. 1855 (1963); Gurnani, Sharma, and Gupta, J. Am. Chem. Soc. 77, 1765 (1972).

Yamamura, Vedejs, and Hirata, Chem. Commun. 1046 (1967); Toda, Hayashi, Hirata, and Yamamura, Bull. Chem. Soc. Jpn. 45, 264 (1972).